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ORIGINAL RESEARCH

Helicobacter pylori Infection and Risk of Chronic Obstructive Pulmonary Disease: A Meta-Analysis and Mendelian Randomization Study

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Background: *Helicobacter pylori* (*H. pylori*) infection and chronic obstructive pulmonary disease (COPD) are both common global public health burdens. Current evidence suggests that *H. pylori* infection may be associated with the development and progression of COPD.

Methods: This study conducted a meta-analysis to systematically evaluate the association between *H. pylori* infection and COPD risk. Eight Chinese and English databases were searched through September 2025. We then performed two-sample Mendelian randomization (MR) using genetic instruments for *H. pylori* antibody phenotypes and COPD GWAS summary statistics to test bidirectional causality.

Results: A total of 27 studies were included, comprising 7159 participants. Compared with controls, COPD patients had a higher *H. pylori* positivity rate (RR = 1.43, 95% CI: 1.25–1.60, $P < 0.00001$). Among COPD patients, *H. pylori* positivity was associated with poorer lung function (FEV_1/FVC: MD = −6.75, 95% CI: −9.17 to −4.34, $P < 0.00001$; FEV_1%: MD = −9.34, 95% CI: −12.61 to −6.07, $P < 0.00001$; FEV_1: MD = −0.16, 95% CI: −0.23 to −0.09, $P < 0.00001$; FVC%: MD = −5.29, 95% CI: −9.76 to −0.81, $P = 0.02$; FVC: MD = −0.15, 95% CI: −0.28 to −0.01, $P = 0.03$). Compared with patients with severe-to-very severe COPD, those with mild-to-moderate COPD had a lower prevalence of *H. pylori* infection (RR = 0.75, 95% CI: 0.59–0.96; P = 0.02). However, the two-sample MR analysis did not find evidence of a bidirectional causal relationship between *H. pylori* antibodies and COPD.

Conclusion: The study shows that *H. pylori* infection is more prevalent among patients with COPD and is associated with reduced lung function and greater disease severity, but no genetic evidence of causality was identified. Therefore, based on current evidence, routine *H. pylori* screening or eradication therapy is not recommended in the general COPD population.

Keywords: pulmonary disease, chronic obstructive, *Helicobacter pylori*, evidence-based medicine, Mendelian randomization analysis

Introduction

COPD is a progressive inflammatory airway disease caused by long-term exposure to toxic particles or harmful gases through active or passive inhalation, leading to small airway injury and destruction of the pulmonary parenchyma accompanied by persistent chronic inflammation.[1] Globally, COPD affects more than 400 million individuals and is the third leading cause of death, with substantial regional disparities in prevalence, risk factors, and temporal trends.[2] By 2050, the number of COPD cases is projected to rise to approximately 592 million, representing a 23.3% relative increase.[3,4] Due to differences in tobacco consumption, educational attainment, indoor and outdoor air pollution, demographic structure, and healthcare accessibility, the burden of COPD in low- and middle-income countries is expected to more than double that in high-income countries.[3,4] With continuous updates in expert consensus and clinical practice guidelines, the prevention and management of COPD have been shifting from disease-centered treatment toward a full life-course health management model,

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emphasizing early screening, early intervention, and forward shifting of preventive strategies.[5] Against this background, chronic infection by inflammatory pathogens has become an important research focus as a potential upstream risk factor for COPD.[6]

The "gut–lung axis" refers to the bidirectional interaction between the gastrointestinal tract and the lungs in immune homeostasis and susceptibility to disease.[7,8] It plays an important role in regulating inflammation in both acute and chronic respiratory diseases. Dysbiosis of the gut microbiota not only damages the gastrointestinal mucosal barrier and local immune function but may also promote the development and progression of COPD through systemic inflammatory mediators and immune signaling pathways.[7,8] In the gastrointestinal tract, *H. pylori* is one of the most prevalent pathogenic bacteria, particularly in Asian populations, where the infection rate is substantially higher.[9] *H. pylori* can chronically colonize the gastric mucosa and elicit local inflammation, accompanied by increased pro-inflammatory cytokines such as IL-6 and TNF-α and higher circulating inflammatory markers including C-reactive protein, consistent with a state of chronic low-grade systemic inflammation.[10] It has shown significant associations with diseases involving the immune, cardiovascular, hepatobiliary, neurologic, hematologic, endocrine, ophthalmologic, and gynecologic systems.[9,10] In the respiratory system, *H. pylori* has increasingly been considered a potential upstream inflammatory trigger in COPD pathogenesis. An observational study including 710 participants reported a markedly higher prevalence of *H. pylori* infection in patients with COPD compared with healthy controls, suggesting that infection may contribute to lung function deterioration in this population.[11] However, another study including 603 participants reported no significant association between *H. pylori* infection and COPD in regions with high infection prevalence and found no meaningful impact on the rate of lung function decline.[12] A previous meta-analysis of observational studies conducted before 2022 suggested a statistical association between *H. pylori* infection and COPD; however, most included participants were individuals with chronic bronchitis or early-stage disease not strictly diagnosed according to current GOLD criteria, and Chinese studies with high infection prevalence were largely absent. Consequently, the findings were limited by regional and representativeness bias, relatively low evidence quality, and a lack of contemporary data.[13]

In recent years, a growing body of evidence has suggested that *H. pylori* infection may be associated with the risk of COPD; however, the available findings remain inconsistent. Meanwhile, differences between Asian and Western populations in *H. pylori* virulence profiles, lifestyle factors, and shared environmental exposures may contribute to geographic heterogeneity across studies, leaving the relationship inconclusive. Given that observational studies are susceptible to confounding by smoking, socioeconomic status, and co-exposures, we first performed a meta-analysis to systematically quantify the strength of the association and then complemented it with bidirectional Mendelian randomization to mitigate confounding and reverse causation, thereby jointly exploring the potential causal link between *H. pylori* infection and COPD risk. If this relationship is further confirmed, it may inform upstream risk management strategies for COPD by motivating the evaluation of *H. pylori* screening and eradication in COPD populations to reduce disease onset or slow progression.

Methods

Search Strategy of Meta-Analysis

This meta-analysis was prospectively registered in PROSPERO (CRD420251166169). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] A comprehensive literature search was performed across eight databases, including PubMed, Embase, the Cochrane Library, Web of Science, CNKI, Wanfang, VIP, and the China Biomedical Literature Database, covering all available records up to September 2025. To minimize the risk of missing potentially eligible studies, supplementary searches were also carried out in Google Scholar, ClinicalTrials.gov, and the Chinese Clinical Trial Registry (ChiCTR). Details of the search strategy are provided in Supplementary Material S1.

Study Selection

Two investigators (YX and JL) independently performed manual literature screening and data extraction, with cross-checking of the results. Any disagreements were resolved through discussion or, when necessary, adjudicated by a third reviewer (JL). The screening process involved an initial assessment of titles and abstracts, followed by full-text review to determine final eligibility.

Eligibility Criteria

The inclusion criteria were as follows: (1) studies evaluating the association between *H. pylori* infection and the risk, prevalence, incidence, or severity of COPD; (2) clearly defined diagnostic methods for *H. pylori*, including serological testing, urea breath test, stool antigen detection, rapid urease test, histological examination, or PCR-based molecular assays; (3) COPD diagnosed according to internationally recognized criteria, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines or International Classification of Diseases (ICD) codes; (4) availability of original data necessary for the outcomes of interest; (5) human population–based studies, including cross-sectional, case–control, or cohort studies published in peer-reviewed journals; (6) no restriction on language.

The exclusion criteria were as follows: (1) reviews, commentaries, conference abstracts without extractable data, case reports, and animal or in vitro studies; (2) studies without clearly reported diagnostic criteria for *H. pylori* or COPD; (3) duplicate publications; when multiple reports involved the same study population, only the most complete or the most recently published version was included.

Quality Assessment

All included studies were assessed using the quality assessment tools for observational studies developed by the National Institutes of Health (NIH).[15] These tools provide respective checklists for cross-sectional, cohort, and case–control study designs, and comprehensively evaluate methodological quality in terms of participant selection, measurement of exposure and outcomes, control of confounding factors, and completeness of reporting. Based on the total score, each study was classified as "good", "fair", or "poor", reflecting its overall risk of bias and internal validity.[15] This approach ensured a more systematic and objective assessment of study quality and strengthened the reliability and robustness of the meta-analysis findings.[15]

Data Synthesis and Analysis

The meta-analysis was conducted using RevMan 5.4 and Stata 15.1 software. For continuous outcomes, the mean difference (MD) with 95% confidence intervals (CI) was used when studies applied the same measurement tool and unit, whereas the standardized mean difference (SMD) was adopted when measurement units or scales differed across studies to improve comparability and robustness.[16] Between-study heterogeneity was initially assessed using Cochran's Q test and the I^2 statistic; however, the choice of statistical model was primarily based on clinical and methodological heterogeneity. A fixed-effects model was applied when the included studies were considered to originate from a common underlying effect with good consistency in population characteristics, exposure/outcome assessment, and study design. When substantial clinical or methodological heterogeneity was present, a random-effects model was used even if the I^2 value was low.[16] In cases of significant heterogeneity, subgroup analyses and/or sensitivity analyses were further performed to explore potential sources. When at least ten studies were available for a given outcome, Egger's test was conducted to assess potential publication bias.[17] If publication bias was detected, the trim-and-fill method was applied to adjust for missing studies and evaluate the robustness of the pooled effect estimates.[18]

Data Sources of Mendelian Randomization

The genetic summary statistics for COPD used in this study were obtained from the FinnGen consortium (Release 12). The dataset included 24,138 COPD cases and 409,070 controls of European ancestry (phenotype code: J10_COPD). COPD was defined based on ICD-coded diagnoses in the Finnish national health registries, and the corresponding GWAS summary statistics are publicly available from the FinnGen database (https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_J10_COPD.gz). Genetic instruments for *H. pylori*–related traits were derived from the serology-based GWAS reported by Butler-Laporte et al, which is indexed in the GWAS Catalog.[19] The study evaluated six *H. pylori*–related antibody phenotypes in European populations, with corresponding sample sizes as follows: anti-*H. pylori* IgG (n = 8735), CagA (n = 985), Catalase (n = 1558), OMP (n = 2640), UREA (n = 2251), and VacA (n = 1571). These antibody phenotypes reflect the host immune response following *H. pylori* colonization and are widely used as genetic proxies for infection status in the construction of exposure variables in Mendelian randomization analyses. To minimize population stratification bias, both exposure and outcome datasets were restricted to individuals of European ancestry.

Selection of Instrumental Variables

In the forward MR analysis (*H. pylori* → COPD), SNPs associated with *H. pylori* exposure were selected using a significance threshold of $P < 5\times10^{-6}$ based on the GWAS summary statistics of the six antibody phenotypes. In the reverse MR analysis (COPD → *H. pylori*), SNPs associated with COPD were selected using the conventional genome-wide significance level of $P < 5\times10^{-8}$. Linkage disequilibrium (LD) clumping was then performed using PLINK (r^2 = 0.001, clumping distance = 10,000 kb) to ensure mutual independence among the selected SNPs. Exposure and outcome datasets were subsequently harmonized by aligning effect alleles to the same reference strand, and palindromic variants were removed to avoid ambiguity in allele orientation.

Statistical Analysis

The inverse-variance weighted (IVW) method was used as the primary approach for causal effect estimation. To assess the robustness of the findings, several complementary MR methods were additionally applied, including the weighted median, MR-Egger regression, Simple mode, and Weighted mode. Heterogeneity was evaluated using Cochran's *Q* statistic, while horizontal pleiotropy was assessed using the MR-Egger intercept and the MR-PRESSO test. A leave-one-out analysis was further conducted to determine whether the results were driven by any single instrumental SNP. To reduce potential confounding bias, we used the LDtrait module of the LDlink platform (https://ldlink.nih.gov/?tab=ldtrait) to annotate the selected SNPs and their high-LD proxies and repeated the analysis after excluding variants strongly associated with smoking behavior, body mass index (BMI), or alcohol consumption. All statistical analyses were performed in RStudio (version 4.2.3).

Results

Meta-Analysis of the Association Between Hp Infection and COPD Risk

Study Selection

A total of 1290 records were initially retrieved based on the search strategy, of which 1010 remained after removal of duplicates. After screening titles and abstracts, 36 articles were selected for full-text review, and 9 were subsequently excluded (3 without relevant outcome data, 1 duplicate publication, 3 with inappropriate control groups, and 2 with confounding comorbidities). Ultimately, 27 studies were included in the meta-analysis. The literature selection process is illustrated in Figure 1.

Basic Characteristics and Quality Assessment

A total of 7159 participants were included across the 27 studies, comprising 4327 patients with COPD and 2832 healthy controls. Among individuals with COPD, 2258 were *H. pylori*–positive and 2069 were *H. pylori*–negative. Of the included studies, six were cohort studies, twenty were case–control studies, and one was a cross-sectional study. Detailed characteristics of the included studies are provided in Supplementary Table S1. Quality assessment indicated that the studies were of moderate to high overall quality (Supplementary Tables S2 and S3).

Higher Prevalence of H. pylori Infection in Patients with COPD Than in Healthy Controls

A total of 17 studies (4209 participants) reported the prevalence of *H. pylori* infection in COPD patients compared with healthy controls. Substantial statistical heterogeneity was observed (I^2 = 69%, $P < 0.1$). Considering both clinical and methodological heterogeneity across studies, a random-effects model was applied. The pooled analysis showed that the prevalence of *H. pylori* infection was significantly higher in patients with COPD than in healthy controls (RR = 1.43, 95% CI: 1.25–1.60, $P < 0.00001$; Figure 2). Sensitivity analysis indicated that the removal of the study by Lee et al[12] reduced heterogeneity considerably (I^2 = 43%, $P > 0.1$), while the association remained essentially unchanged (RR = 1.46, 95% CI: 1.34–1.59, $P < 0.00001$), suggesting that the observed heterogeneity was acceptable subgroup analyses by region showed consistently higher *H. pylori* positivity among COPD patients compared with controls in Asia, MENA countries, and other regions ($P < 0.001$ for all). As more than ten studies were included, Egger's test was conducted (P = 0.021), indicating the presence of publication bias (Supplementary Figure S1). Trim-and-fill analysis imputed six potentially missing studies, and the adjusted pooled estimate under the random-effects model remained statistically

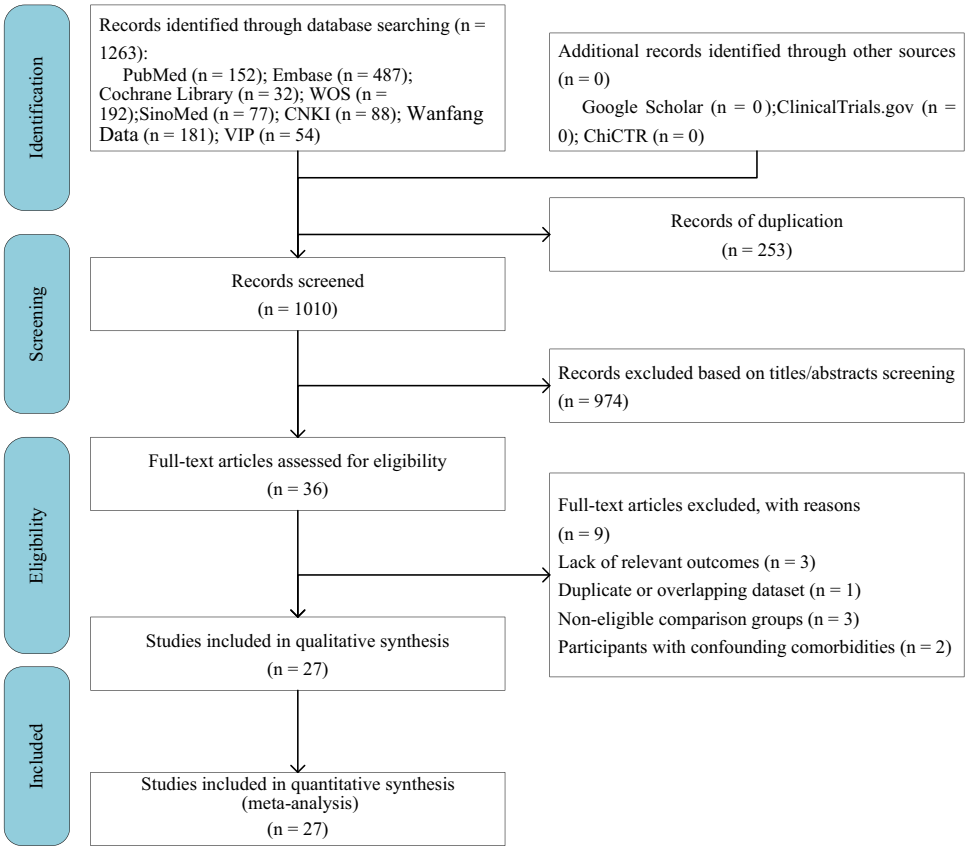

Figure 1 Flow diagram of study selection based on the PRISMA guidelines.

significant (RR = 1.165, 95% CI: 1.068–1.272), confirming the robustness of the association between *H. pylori* infection and COPD risk (Supplementary Figure S2).

Elevated H. pylori-Related Serological Markers in Patients with COPD Compared with Healthy Controls

IgG

Six studies (1399 participants) reported serum IgG levels in COPD patients and healthy controls. Substantial statistical heterogeneity was observed ($I^2 = 99\%$, $P < 0.1$); therefore, a random-effects model was applied, taking into account clinical and methodological heterogeneity among the included studies. The pooled analysis showed that serum IgG levels were significantly higher in the COPD group than in the healthy control group (SMD = 2.08, 95% CI: 0.62–3.55, $P = 0.005$; Figure 3). Sensitivity analysis did not identify a clear source of heterogeneity.

CagA

Three studies (497 participants) reported serum CagA levels in COPD patients compared with healthy controls. Heterogeneity was low ($I^2 = 27\%$, $P > 0.1$), and a fixed-effects model was therefore applied. The pooled analysis demonstrated that serum CagA levels were significantly higher in the COPD group than in the healthy control group (MD = 15.12, 95% CI: 14.65–15.60, $P < 0.00001$; Figure 4).

Association Between H. pylori Infection and Impaired Lung Function in COPD

FEV_1/FVC

Sixteen studies (3068 participants) reported FEV_1/FVC values in *H. pylori*-positive versus *H. pylori*-negative COPD patients. Substantial statistical heterogeneity was observed ($I^2 = 95\%$, $P < 0.1$), and a random-effects model was therefore applied. The pooled analysis showed that FEV_1/FVC was significantly lower in the *H. pylori*-positive group compared with the *H. pylori*-negative group (MD = −6.75, 95% CI: −9.17 to −4.34, $P < 0.00001$; Figure 5). Sensitivity analysis did

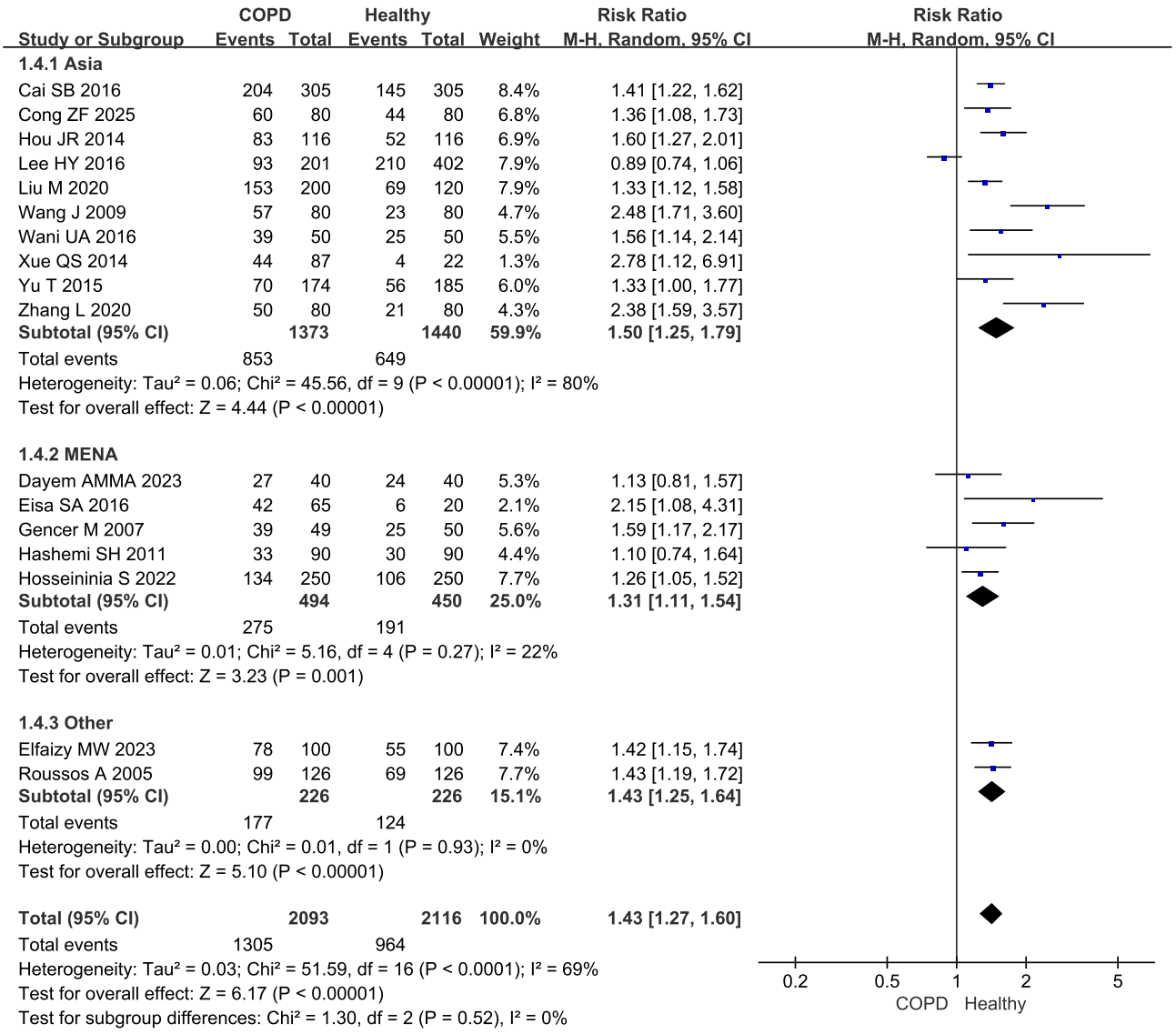

Figure 2 Forest plot comparing the prevalence of *Helicobacter pylori* infection between COPD patients and healthy individuals.

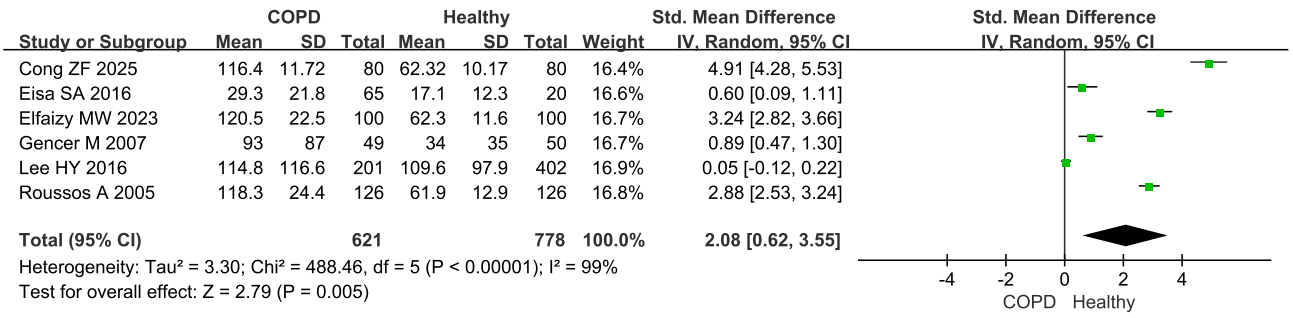

Figure 3 Forest plot comparing serum *H. pylori*-specific IgG levels between COPD patients and healthy controls.

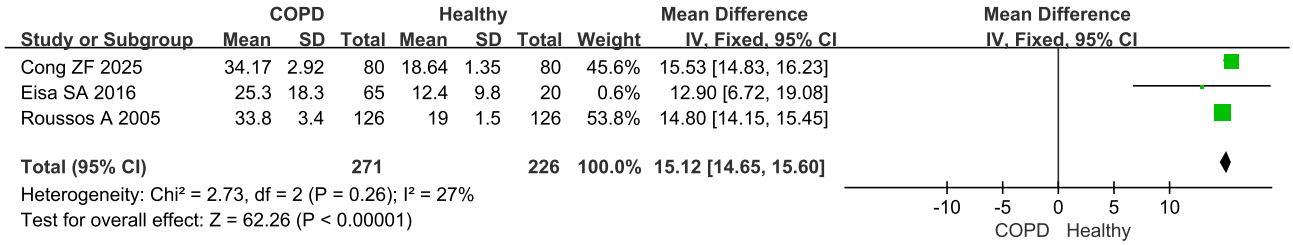

Figure 4 Forest plot comparing serum *H. pylori*-specific CagA levels between COPD patients and healthy controls.

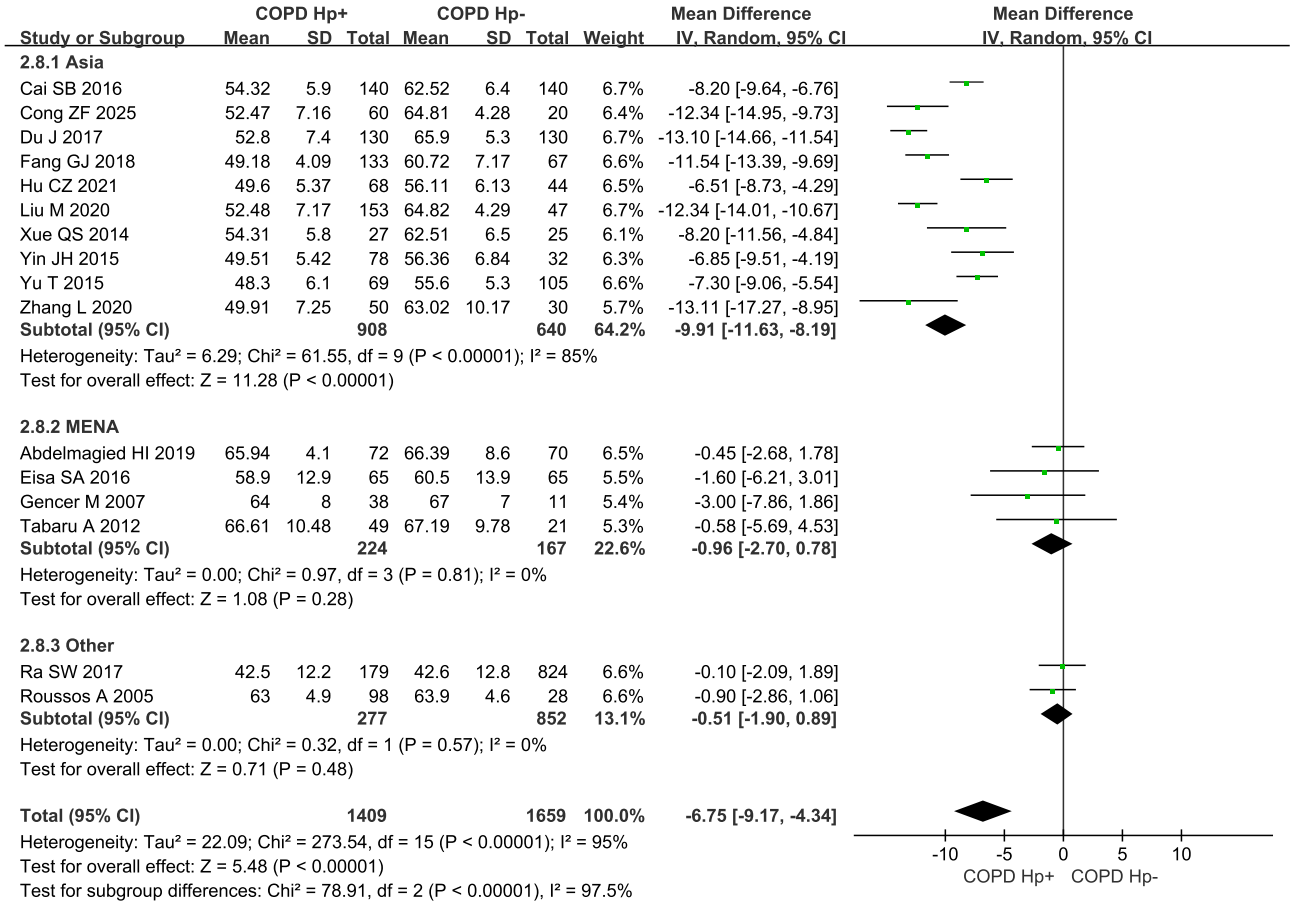

Figure 5 Forest plot of FEV_1/FVC comparing *H. pylori*-positive and *H. pylori*-negative COPD patients (with subgroup analyses by region).

not identify a distinct source of heterogeneity. Subgroup analysis revealed that the reduction in FEV_1/FVC was significant only in studies conducted in Asia ($P < 0.00001$). As more than 10 studies were included, Egger's test was performed ($P = 0.307$), indicating no evidence of publication bias (Supplementary Figure S3).

FEV_1%

Nineteen studies (3387 participants) reported FEV_1% in *H. pylori*-positive versus *H. pylori*-negative COPD patients. Substantial heterogeneity was observed ($I^2 = 97\%$, $P < 0.1$), and a random-effects model was therefore applied. The pooled results showed that FEV_1% was significantly lower in the *H. pylori*-positive group compared with the *H. pylori*-negative group (MD = −9.34, 95% CI: −12.61 to −6.07, $P < 0.00001$; Figure 6). Sensitivity analysis did not identify a clear source of heterogeneity. Subgroup analysis indicated that this association was significant only in studies

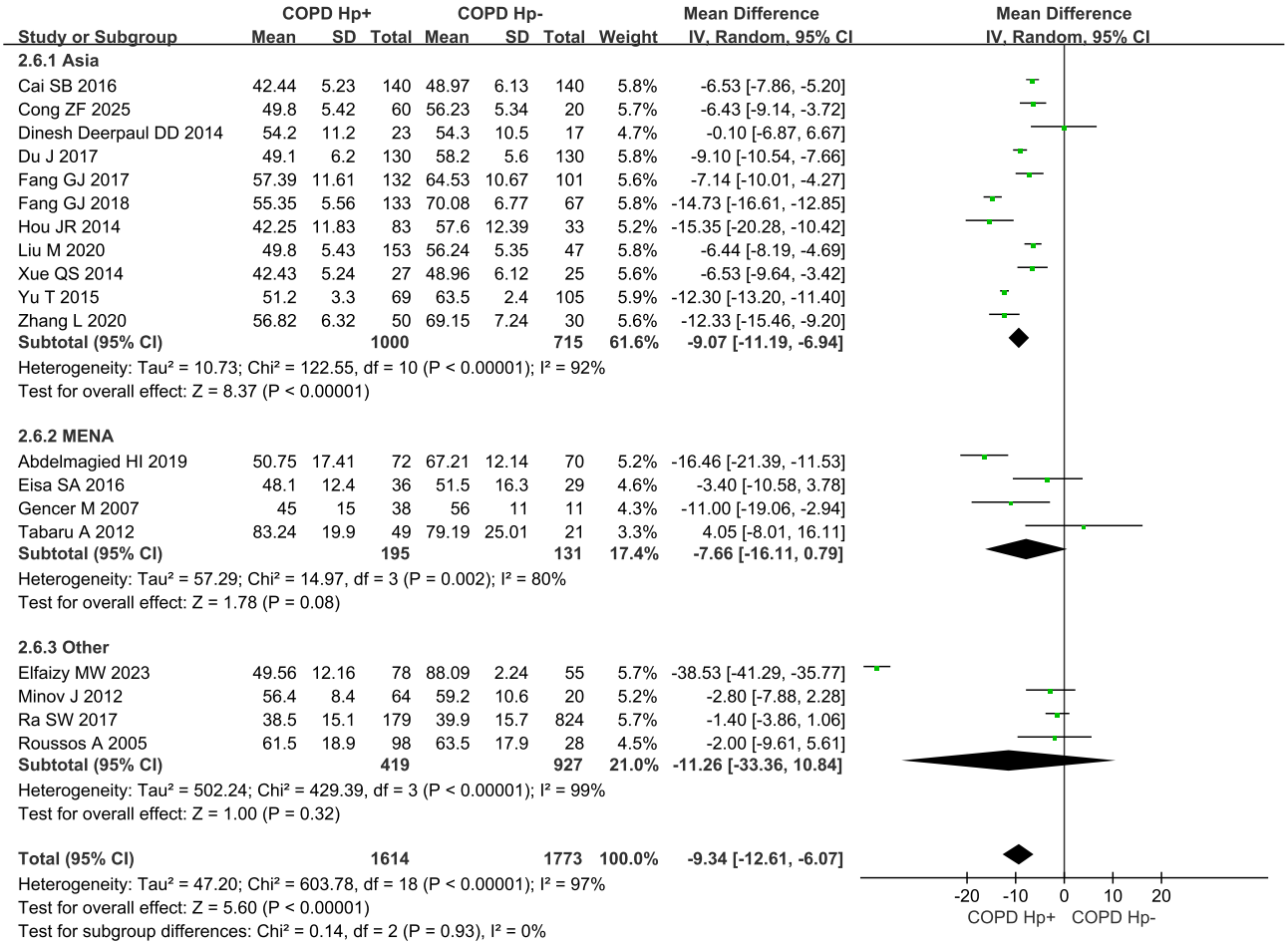

Figure 6 Forest plot of FEV_1% comparing *H. pylori*-positive and *H. pylori*-negative COPD patients (with subgroup analyses by region).

conducted in Asia ($P < 0.00001$). As more than ten studies were included, Egger's test was performed ($P = 0.744$), suggesting no evidence of publication bias (Supplementary Figure S4).

FEV_1

Seven studies (1845 participants) reported FEV_1 in *H. pylori*-positive and *H. pylori*-negative COPD patients. Moderate heterogeneity was observed ($I^2 = 65\%$, $P < 0.1$), and a random-effects model was applied. The pooled analysis demonstrated that FEV_1 was significantly lower in the *H. pylori*-positive group compared with the *H. pylori*-negative group (MD = −0.16, 95% CI: −0.23 to −0.09, $P < 0.00001$; Figure 7). Sensitivity analysis showed that exclusion of the study by Ra et al[20] substantially reduced heterogeneity ($I^2 = 0\%$, $P < 0.1$), while the association remained stable (MD = −0.19, 95% CI: −0.23 to −0.15, $P < 0.00001$), indicating that the observed heterogeneity was acceptable.

FVC%

Ten studies (2087 participants) reported FVC% in *H. pylori*-positive and *H. pylori*-negative COPD patients. Substantial heterogeneity was detected ($I^2 = 95\%$, $P < 0.1$), and a random-effects model was therefore applied. The pooled results indicated that FVC% was significantly lower in the *H. pylori*-positive group compared with the *H. pylori*-negative group (MD = −5.29, 95% CI: −9.76 to −0.81, $P = 0.02$; Figure 8). Sensitivity analysis did not identify a clear source of heterogeneity. As ten or more studies were included, Egger's test was performed ($P = 0.858$), showing no evidence of publication bias (Supplementary Figure S5).

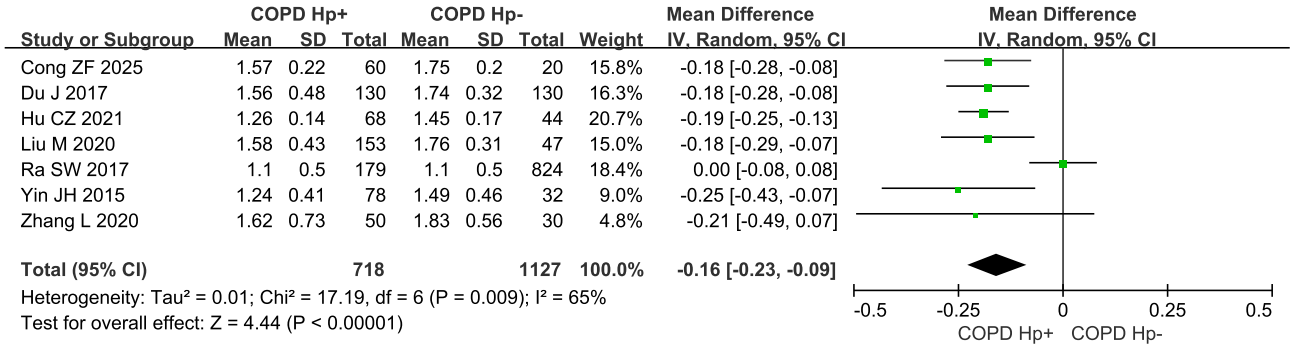

Figure 7 Forest plot of FEV_1 comparing *H. pylori*-positive and *H. pylori*-negative COPD patients (with subgroup analyses by region).

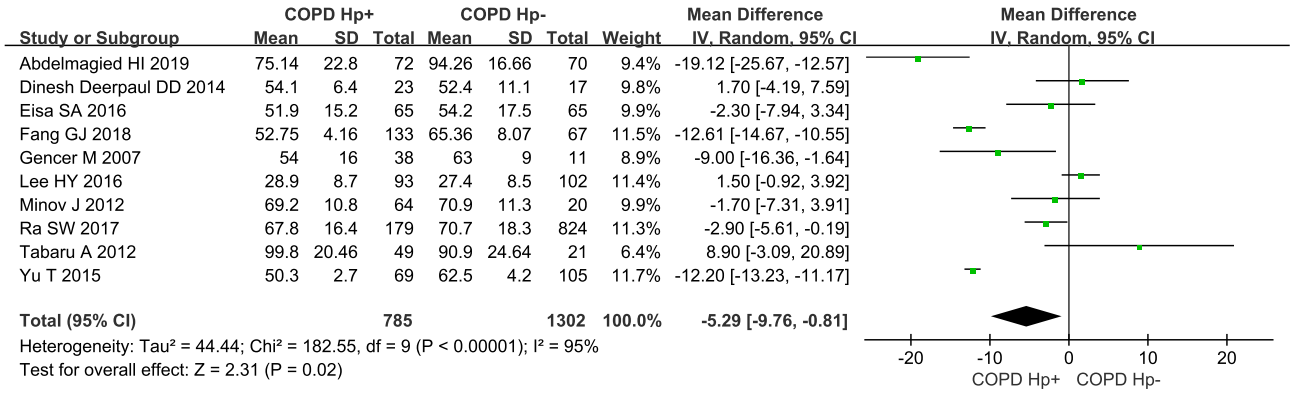

Figure 8 Forest plot of FVC% comparing *H. pylori*-positive and *H. pylori*-negative COPD patients (with subgroup analyses by region).

FVC

Four studies (1295 participants) reported FVC in *H. pylori*-positive and *H. pylori*-negative COPD patients. Moderate heterogeneity was observed (I^2 = 60%, P < 0.1), and a random-effects model was therefore applied. The pooled analysis showed that FVC was significantly lower in the *H. pylori*-positive group compared with the *H. pylori*-negative group (MD = −0.15, 95% CI: −0.28 to −0.01, P = 0.03; Figure 9). Sensitivity analysis indicated that exclusion of the study by Tabaru et al[21] reduced heterogeneity substantially (I^2 = 35%, P > 0.1), while the effect estimate remained largely unchanged (MD = −0.17, 95% CI: −0.27 to −0.08, P = 0.0004), indicating that the heterogeneity was acceptable.

Association Between H. pylori Positivity and COPD Severity

Five studies (1534 participants) compared *H. pylori* positivity between patients with mild-to-moderate COPD and those with severe-to-very severe COPD. Substantial heterogeneity was observed (I^2 = 60%, P < 0.1), and a random-effects model was therefore applied. The pooled results showed that *H. pylori* positivity was significantly lower in the mild-to-

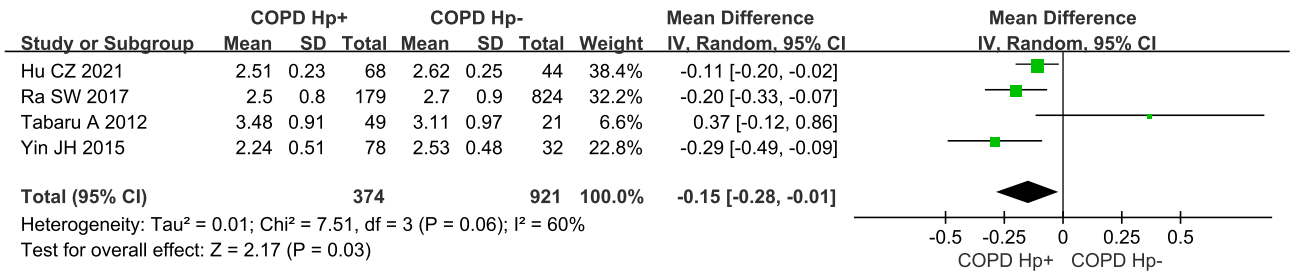

Figure 9 Forest plot of FVC comparing *H. pylori*-positive and *H. pylori*-negative COPD patients (with subgroup analyses by region).

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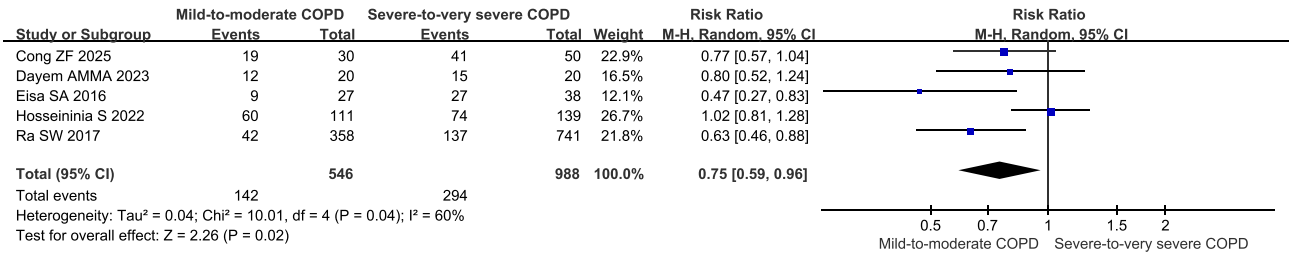

Figure 10 Forest plot of the association between *H. pylori* infection and COPD severity.

moderate COPD group compared with the severe-to-very severe group (RR = 0.75, 95% CI: 0.59–0.96, P = 0.02; Figure 10). Sensitivity analysis indicated that exclusion of the study by Hosseininia et al[22] markedly reduced heterogeneity (I^2 = 10%, P > 0.1), while the association remained stable (RR = 0.69, 95% CI: 0.56–0.84, P = 0.0002), confirming that the heterogeneity was acceptable.

MR Analysis of the Association Between H. pylori Infection and COPD Risk

Study Overview

This section was designed in two steps. First, we assessed whether *H. pylori* infection, represented by six antibody-based phenotypes, had a causal effect on COPD (Step 1, Table 1). Second, we evaluated the reverse direction, examining whether COPD exerted a causal influence on *H. pylori* infection (Step 2).

Causal Effect of Hp Infection (Six Antibodies) on COPD

In the Mendelian randomization analysis (Step 1), no evidence of a causal relationship was observed between genetically predicted *H. pylori* infection (based on the six antibody phenotypes) and COPD risk. The results were consistent across all MR approaches, including IVW, weighted median, MR-Egger regression, Simple mode, and Weighted mode. In the primary IVW analysis, the odds ratios (95% CI) for the six antibodies were as follows: IgG 1.03 (0.97–1.08), CagA 0.99 (0.95–1.03), Catalase 0.96 (0.92–1.01), OMP 1.01 (0.96–1.08), UREA 0.99 (0.95–1.04), and VacA 0.99 (0.96–1.02), with all P values > 0.05 (Table 1). These findings indicate that *H. pylori* infection does not exert a significant causal effect on COPD. Heterogeneity tests and MR-Egger intercepts did not suggest violations of MR assumptions, supporting the consistency of instrument effects and the absence of directional horizontal pleiotropy. The corresponding MR scatter plots, forest plots, funnel plots, and leave-one-out analyses are presented in Supplementary Figures S6–S9.

Reverse Causal Effect of COPD on Hp Infection (Six Antibodies)

In the reverse Mendelian randomization analysis (Step 2), no evidence of a causal relationship was found between genetically predicted COPD and any of the six *H. pylori*–related antibody phenotypes. The results were consistent across all MR approaches, including IVW, weighted median, MR-Egger regression, Simple mode, and Weighted mode. In the primary IVW analysis, the odds ratios (95% CI) for the effect of COPD on each antibody phenotype were as follows: IgG 0.99 (0.81–1.21), CagA 0.99 (0.75–1.27), Catalase 0.89 (0.72–1.09), OMP 0.98 (0.82–1.17), UREA 1.01 (0.85–1.20), and VacA 0.86 (0.70–1.06), with all P values > 0.05 (Table 2). These findings indicate that COPD does not exert a significant causal effect on *H. pylori* antibody levels. Heterogeneity tests and MR-Egger intercepts did not reveal evidence of bias, supporting the consistency of the instrumental variables and the absence of directional horizontal pleiotropy. The corresponding MR scatter plots, forest plots, funnel plots, and leave-one-out sensitivity analyses are shown in Supplementary Figures S10–S13.

General Criteria for Assessing the Significance of Results

In this study, the IVW method was prespecified as the primary analysis, and multiple testing correction was applied only across the six main hypotheses per direction. Accordingly, a Bonferroni-corrected significance threshold of $\alpha = 0.05/6 = 8.3\times10^{-3}$ was used for each direction. A causal effect was considered significant only when all of the following criteria were simultaneously fulfilled: (1) the IVW P value was below the Bonferroni-corrected threshold; (2) the direction of

Table 1 Mendelian Randomization Analysis of *H. pylori* Infection-Related Antibodies on COPD

Exposure	Outcome	Inverse Variance Weighted		Weighted Median		MR Egger		Simple Mode		Weighted Mode	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
IgG	COPD	1.03(0.97, 1.08)	0.351	1.01(0.96, 1.07)	0.660	1.03(0.87, 1.22)	0.703	1.03(0.93, 1.13)	0.587	1.00(0.93, 1.09)	0.842
CagA		0.99(0.95, 1.03)	0.755	0.99(0.94, 1.04)	0.640	1.07(0.90, 1.27)	0.494	0.96(0.89, 1.04)	0.431	0.97(0.90, 1.05)	0.491
Catalase		0.96(0.92, 1.01)	0.10	0.99(0.94, 1.04)	0.646	0.96(0.88, 1.04)	0.348	1.00(0.92, 1.08)	0.91	1.00(0.938, 1.07)	0.935
OMP		1.01(0.96, 1.08)	0.63	1.02(0.95, 1.10)	0.577	1.02(0.87, 1.18)	0.845	1.06(0.92, 1.21)	0.445	1.08(0.95, 1.23)	0.299
UREA		0.99(0.95, 1.04)	0.720	0.99(0.94, 1.05)	0.76	0.95(0.84, 1.07)	0.414	0.99(0.92, 1.07)	0.844	0.99(0.93, 1.06)	0.862
VacA		0.99(0.96, 1.02)	0.545	0.99(0.96, 1.03)	0.759	0.97(0.91, 1.03)	0.290	1.01(0.96, 1.07)	0.698	1.00(0.96, 1.04)	0.954

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Table 2 Mendelian Randomization Analysis of COPD on *H. pylori* Infection-Related Antibodies

Exposure	Outcome	Inverse Variance Weighted		Weighted Median		MR Egger		Simple Mode		Weighted Mode	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
COPD	IgG	0.99(0.81, 1.21)	0.936	0.98(0.75, 1.27)	0.864	0.75(0.50, 1.15)	0.203	1.19(0.71, 2.00)	0.504	0.83(0.62, 1.12)	0.504
	CagA	0.98(0.75, 1.27)	0.862	0.88(0.59, 1.30)	0.516	1.01(0.57, 1.79)	0.964	1.24(0.64, 2.40)	0.532	0.90(0.60, 1.34)	0.598
	Catalase	0.89(0.72, 1.09)	0.262	1.03(0.76, 1.39)	0.838	0.94(0.61, 1.47)	0.803	0.73(0.41, 1.31)	0.301	1.04(0.74, 1.45)	0.838
	OMP	0.98(0.82, 1.17)	0.834	0.90(0.71, 1.15)	0.391	0.93(0.63, 1.37)	0.725	0.80(0.51, 1.27)	0.354	0.87(0.67, 1.12)	0.279
	UREA	1.01(0.85, 1.20)	0.916	0.83(0.65, 1.06)	0.134	0.92(0.64, 1.32)	0.649	1.22(0.74, 2.01)	0.446	0.85(0.64, 1.14)	0.300
	VacA	0.86(0.70, 1.06)	0.154	0.90(0.66, 1.25)	0.538	1.14(0.73, 1.79)	0.568	0.84(0.46, 1.50)	0.553	0.91(0.65, 1.28)	0.601

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effect was consistent across sensitivity methods (weighted median, MR-Egger, Simple mode, and Weighted mode); (3) no evidence of horizontal pleiotropy was detected (MR-Egger intercept and MR-PRESSO global test both $P > 0.05$); (4) heterogeneity based on Cochran's Q was acceptable; where heterogeneity was present, multiplicative random-effects IVW estimates were reported; and (5) robustness was further supported by single-SNP, leave-one-out, and funnel plot analyses. Effect estimates were expressed as odds ratios (ORs) with 95% confidence intervals. All MR analyses were performed in R version 4.2.3 (http://r-project.org/) using the "TwoSampleMR" and "gsmr" packages.

Discussion

To the best of our knowledge, this is the first study to simultaneously apply both meta-analysis and Mendelian randomization to evaluate the relationship between *H. pylori* infection and COPD. The meta-analysis demonstrated that the prevalence of *H. pylori* infection was consistently higher in patients with COPD than in healthy individuals, and that *H. pylori*–related serological markers were elevated in the COPD population. Among patients with COPD, *H. pylori* positivity was associated with poorer lung function and greater disease severity. Although publication bias was detected, trim-and-fill analyses confirmed the robustness of the association. However, in the MR analyses, neither the forward nor reverse direction supported a causal effect of *H. pylori* infection on COPD risk, nor a causal influence of COPD on *H. pylori* antibody levels, with consistent results across multiple sensitivity methods. Collectively, these findings suggest a robust observational correlation but no genetically proxied causal relationship, indicating that the association may be explained by non-genetic mechanisms, shared risk factors, or disease-related comorbid pathways.

The non-genetic mechanisms underlying the association between *H. pylori* infection and COPD remain uncertain, with proposed explanations primarily centered on the "gut–lung axis" and the "multiple-hit hypothesis".[23,24] *H. pylori* is a microaerophilic Gram-negative curved bacillus with flagella and strong urease activity, features that allow it to persist in the hostile gastric microenvironment and partially colonize the intestinal tract.[25,26] The gastrointestinal microbiota represents one of the body's largest immune interfaces and plays a central role in immunological defense, metabolic regulation, and immune tolerance. A healthy microbial ecosystem modulates T helper cell differentiation, induces B-cell responses, and promotes the production of cytokines and immunoglobulins, thereby maintaining mucosal homeostasis and exerting local anti-inflammatory effects.[27,28] During *H. pylori* infection, microbial dysbiosis and the release of virulence factors can activate systemic inflammatory responses. Circulating inflammatory mediators may subsequently reach the lungs and, under conditions of impaired anti-inflammatory capacity, contribute to COPD progression through a "multi-hit" inflammatory cascade.[7] In addition, COPD is frequently accompanied by chronic hypoxia. Hypoxia and oxidative stress can disrupt gastrointestinal function, while the long-term use of glucocorticoids or theophylline further weakens mucosal defense barriers, creating a favorable environment for *H. pylori* colonization and perpetuating a vicious cycle between infection and disease progression.[29,30] Some observational studies have reported symptomatic improvement and partial recovery of lung function following successful *H. pylori* eradication in patients with chronic persistent cough, suggesting its potential involvement in specific inflammatory respiratory phenotypes.[31] However, the MR findings of the present study did not support a causal relationship between *H. pylori* infection and COPD risk. Given the higher hierarchy of causal inference embodied in MR approaches, the current evidence does not justify routine screening or eradication of *H. pylori* in COPD patients solely for the purpose of improving lung function or slowing disease progression. Further high-quality randomized controlled trials in COPD-specific populations are warranted to clarify potential clinical benefits.

Subgroup analyses by region in the meta-analysis further showed that although the prevalence of *H. pylori* infection was higher among COPD patients than healthy controls across all regions, impairment in lung function among *H. pylori*-positive patients was observed only in the Asian subgroup. Most studies within this subgroup were conducted in China, where nearly 100 million individuals are affected by COPD, accounting for approximately one-quarter of all global cases. A meta-analysis conducted in 2024 estimated the prevalence of *H. pylori* infection in mainland China at 42.8%.[32] In addition, multiple epidemiological studies have shown that the proportion of highly virulent *H. pylori* strains, such as CagA-positive or VacA s1/m1 variants, is significantly higher in Asian populations than in Western countries.[33,34] These virulence factors enhance immune activation and systemic inflammation by upregulating mediators such as IL-1β, IL-6, and TNF-α, thereby imposing an additional inflammatory burden on the airways and lung parenchyma.[35,36] Taken

together with potential non-genetic mechanisms, these observations may explain why *H. pylori*–positive COPD patients in Asia exhibited lower lung function than *H. pylori*–negative individuals. Nationwide retrospective cohort data from the Korean National Health Insurance database further identified older age (≥65 years) and current smoking as major risk factors for co-occurrence of *H. pylori* infection and COPD.[37] Other studies have also reported low socioeconomic status and rural residence as important shared risk determinants.[38] These overlapping risk profiles may partially account for the higher *H. pylori* positivity observed in COPD patients in observational studies. Therefore, although the present findings suggest a clinical correlation between *H. pylori* infection and COPD severity, the lack of genetic causal evidence from MR analysis indicates that current evidence is insufficient to support routine *H. pylori* screening or eradication therapy in the general COPD population. Instead, clinical management should focus on risk stratification and mitigation of shared environmental or lifestyle exposures among high-risk subgroups.

This study has several limitations. First, although the meta-analysis included data from ten countries and provided geographically broad coverage, all included studies were observational in nature, generally lacked long-term follow-up and temporal sequence evidence, and therefore cannot establish causality. Many studies were single-center or small-sample designs, and residual confounding from key factors such as smoking, environmental pollution, and socio-economic status could not be fully excluded. Second, due to the limited number of eligible studies, subgroup analyses by *H. pylori* detection method could not be conducted. Differences in diagnostic techniques and cut-off values across countries and regions may have contributed to heterogeneity. Third, the Asian subgroup was predominantly composed of studies from China, limiting regional generalizability; variations in strain distribution, exposure intensity, and background infection ecology may influence extrapolation of the results. Fourth, the GWAS sample sizes for several serology-based *H. pylori* antibody phenotypes used as exposures in the MR analysis were relatively limited, which may reduce statistical power to detect modest causal effects and increase susceptibility to weak-instrument bias and false-negative findings; therefore, the null MR results should be interpreted cautiously. Finally, MR analysis reflects genetic liability to long-term predisposition to *H. pylori* infection rather than actual infection status, and our analysis was restricted to individuals of European ancestry, which may reduce statistical power and limit generalizability to other populations. In addition, the available instruments may not fully capture heterogeneity in strain virulence.

Conclusion

This study combined a systematic meta-analysis with bidirectional Mendelian randomization (MR) to comprehensively evaluate both the association and potential causality between *Helicobacter pylori* (*H. pylori*) infection and COPD. The meta-analysis showed a significantly higher prevalence of *H. pylori* positivity in patients with COPD than in healthy controls, accompanied by elevated serological markers. Among individuals with COPD, *H. pylori*–positive patients exhibited poorer lung function and a higher risk of severe disease. However, the Mendelian randomization analyses using European-ancestry genetic instruments did not support a causal effect of *H. pylori* infection on COPD risk, and the findings were consistent across multiple sensitivity analyses; nevertheless, their generalizability to Asian populations where *H. pylori* prevalence is high may be limited. Accordingly, although observational evidence suggests an association between *H. pylori* infection and COPD progression, current evidence is insufficient to recommend routine *H. pylori* screening or eradication therapy in the general COPD population, given the lack of causal support, unproven clinical benefit for COPD-related outcomes, and concerns regarding potential effect heterogeneity and antimicrobial resistance. Clinical strategies should instead prioritize risk stratification and targeted exposure control in high-risk subgroups. Future research should aim to further clarify the relationship between *H. pylori* infection and COPD by: (1) conducting large-scale, multi-regional prospective cohorts and multicenter randomized controlled trials to evaluate the impact of *H. pylori* eradication on exacerbation rates, lung function decline, and quality of life; (2) applying standardized diagnostic criteria for *H. pylori* and GOLD-based COPD classification with rigorous control of key confounders such as smoking, air pollution, BMI, and socioeconomic status; (3) strengthening stratified analyses and incorporating *H. pylori* virulence typing alongside host genetic susceptibility profiles; and (4) establishing reproducible biomarker spectra and mechanistic evidence chains within the framework of the gut–lung axis.

Data Sharing Statement

The data used in this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

References

1. Xu J, Zeng Q, Li S, et al. Inflammation mechanism and research progress of COPD. *Front Immunol*. 2024;15:1404615. doi:10.3389/fimmu.2024.1404615
2. de Oca MM, Perez-Padilla R, Celli B, et al. The global burden of COPD: epidemiology and effect of prevention strategies. *Lancet Respir Med*. 2025;13(8):709–724. doi:10.1016/S2213-2600(24)00339-4
3. Boers E, Barrett M, Su JG, et al. Global burden of chronic obstructive pulmonary disease through 2050. *JAMA Network Open*. 2023;6(12):e2346598. doi:10.1001/jamanetworkopen.2023.46598
4. Garcia Castillo E, Alonso Perez T, Pelaez A, et al. Prevalence of chronic obstructive pulmonary disease in an urban area. Changes in COPD ten years on. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2431–2441. doi:10.2147/COPD.S377140
5. Faner R, Cho MH, Koppelman GH, et al. Towards early detection and disease interception of COPD across the lifespan. *Eur Respir Rev*. 2025;34(177):240243. doi:10.1183/16000617.0243-2024
6. Durazzo M, Adriani A, Fagoonee S, et al. Helicobacter pylori and respiratory diseases: 2021 update. *Microorganisms*. 2021;9(10):2033. doi:10.3390/microorganisms9102033
7. Ananya FN, Ahammed MR, Fahem MM, et al. Association of intestinal microbial dysbiosis with chronic obstructive pulmonary disease. *Cureus*. 2021;13(11):e19343. doi:10.7759/cureus.19343
8. Jang YO, Kim O, Kim SJ, et al. High-fiber diets attenuate emphysema development via modulation of gut microbiota and metabolism. *Sci Rep*. 2021;11(1):7008. doi:10.1038/s41598-021-86404-x
9. Sze MA, Chen YR, Tam S, et al. The relationship between Helicobacter pylori seropositivity and COPD. *Thorax*. 2015;70(10):923–929. doi:10.1136/thoraxjnl-2015-207059
10. Pellicano R, Ianiro G, Fagoonee S, et al. Review: extragastric diseases and Helicobacter pylori. *Helicobacter*. 2020;25 Suppl 1(S1):e12741. doi:10.1111/hel.12741
11. Cai SB. Helicobacter pylori infection and chronic obstructive pulmonary disease. *Guangdong Med J*. 2016;37(S1):117–118.
12. Lee HY, Kim JW, Lee JK, et al. Association between Helicobacter pylori seropositivity and mild to moderate COPD: clinical implications in an Asian country with a high prevalence of H. pylori. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2055–2062. doi:10.2147/COPD.S106922
13. Gonzalez-Saitz A, Diez-Manglano J. Helicobacter pylori infection in patients with chronic obstructive pulmonary disease. A systematic review and meta-analysis. *Rev Clin Esp*. 2025;225(4):193–203. doi:10.1016/j.rceng.2024.12.004
14. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. doi:10.1136/bmj.n160
15. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015;68(11):1312–1324. doi:10.1016/j.jclinepi.2014.11.023
16. IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14(1):25. doi:10.1186/1471-2288-14-25
17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634. doi:10.1136/bmj.315.7109.629
18. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2018;74(3):785–794. doi:10.1111/biom.12817
19. Butler-Laporte G, Kreuzer D, Nakanishi T, et al. Genetic determinants of antibody-mediated immune responses to infectious diseases agents: a genome-wide and HLA association study. *Open Forum Infect Dis*. 2020;7(11):ofaa450. doi:10.1093/ofid/ofaa450
20. Ra SW, Sze MA, Lee EC, et al. Azithromycin and risk of COPD exacerbations in patients with and without Helicobacter pylori. *Respir Res*. 2017;18(1):109. doi:10.1186/s12931-017-0594-x
21. Tabaru A, Gorguner M, Akgun M, et al. Helicobacter pylori infections in chronic obstructive pulmonary disease. *Eurasian J Med*. 2012;44(3):144–148. doi:10.5152/eajm.2012.34
22. Hosseininia S, Mohammadi-Kebar S, Pourfarzi F, et al. Association of Helicobacter pylori infection with chronic obstructive pulmonary disease. *Immunopathologia Persa*. 2022. doi:10.34172/ipp.2022.32412
23. Pavord ID, Birring SS, Berry M, et al. Multiple inflammatory hits and the pathogenesis of severe airway disease. *Eur Respir J*. 2006;27(5):884–888. doi:10.1183/09031936.06.00128105
24. Wang L, Cai Y, Garssen J, et al. The bidirectional gut-lung axis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2023;207(9):1145–1160. doi:10.1164/rccm.202206-1066TR
25. Clyne M, O Croinin T. Pathogenicity and virulence of Helicobacter pylori: a paradigm of chronic infection. *Virulence*. 2025;16(1):2438735. doi:10.1080/21505594.2024.2438735
26. Tourrette E, Torres RC, Svensson SL, et al. An ancient ecospecies of Helicobacter pylori. *Nature*. 2024;635(8037):178–185. doi:10.1038/s41586-024-07991-z

27. Senchukova MA. Microbiota of the gastrointestinal tract: friend or foe? *World J Gastroenterol*. 2023;29(1):19–42. doi:10.3748/wjg.v29.i1.19
28. Shan Y, Lee M, Chang EB. The gut microbiome and inflammatory bowel diseases. *Annu Rev Med*. 2022;73(1):455–468. doi:10.1146/annurev-med-042320-021020
29. Dvornikova KA, Platonova ON, Bystrova EY. Hypoxia and intestinal inflammation: common molecular mechanisms and signaling pathways. *Int J Mol Sci*. 2023;24(3):2425. doi:10.3390/ijms24032425
30. Song X, Dou X, Chang J, et al. The role and mechanism of gut-lung axis mediated bidirectional communication in the occurrence and development of chronic obstructive pulmonary disease. *Gut Microbes*. 2024;16(1):2414805. doi:10.1080/19490976.2024.2414805
31. He M, Zheng Y, Ma A, et al. Helicobacter pylori is associated with weakened pulmonary function and reduced incidence of allergic conditions in patients with chronic cough. *Exp Ther Med*. 2020;20(5):47. doi:10.3892/etm.2020.9176
32. Wang F, Liu J, Zhang Y, et al. Association of Helicobacter pylori infection with chronic obstructive pulmonary disease and chronic bronchitis: a meta-analysis of 16 studies. *Infect Dis*. 2015;47(9):597–603. doi:10.3109/00365548.2014.989539
33. Ansari S, Yamaoka Y. Helicobacter pylori virulence factors exploiting gastric colonization and its pathogenicity. *Toxins*. 2019;11(11):677. doi:10.3390/toxins11110677
34. Camilo V, Sugiyama T, Touati E. Pathogenesis of Helicobacter pylori infection. *Helicobacter*. 2017;22 Suppl 1. doi:10.1111/hel.12405
35. Abdullah M, Greenfield LK, Bronte-Tinkew D, et al. VacA promotes CagA accumulation in gastric epithelial cells during Helicobacter pylori infection. *Sci Rep*. 2019;9(1):38. doi:10.1038/s41598-018-37095-4
36. Xu S, Wu X, Zhang X, et al. CagA orchestrates eEF1A1 and PKCdelta to induce interleukin-6 expression in Helicobacter pylori-infected gastric epithelial cells. *Gut Pathog*. 2020;12(1):31. doi:10.1186/s13099-020-00368-3
37. Chung C, Lee KN, Han K, et al. Helicobacter pylori infection is associated with an increased risk of chronic obstructive pulmonary disease and asthma. *Gut Pathog*. 2025;17(1):75. doi:10.1186/s13099-025-00754-9
38. Hashemi SH, Nadi E, Hajilooi M, et al. Relationship between Helicobacter pylori infection and chronic obstructive pulmonary disease. *Acta Med Iran*. 2011;49(11):721–724.